REMARKS

Claims 1, 3-12, and 14-19 are currently pending. Claim 1 is amended pursuant to the Examiner's suggestion in the Office Action mailed 7 October 2004; claim 3 is amended for clarity and antecedent basis.

35 U.S.C. §112, first paragraph

The Examiner rejected Claims 1, 5-12, and 16-19 under 35 U.S.C. §112, first paragraph, based on an alleged lack of written description and/or enablement relating to the genus of non-sequence specific immunostimulatory sequences. Without acquiescing to the Examiner's rejection, in the interest of expediting the prosecution of the current case, and expressly reserving the right to pursue similar claims in a future case, Applicants have adopted the Examiner's suggestion and amended Claim 1 to recite that the non-sequence specific immunostimulatory sequence includes at least one CpG motif or palindromic sequence, thereby obviating the rejection. Applicants submit that amended claim 1, and claims 3, 5-12, and 16-19 dependent thereon, are in full compliance with 35 U.S.C. §112, first paragraph.

35 U.S.C. §103(a)

The Examiner has rejected claims 1, 3, 5-8, 11, 14, and 16-19 under 35 U.S.C. §103(a) as being obvious over Krieg (U.S. 6,207,646) or Krieg (U.S. 6,429,199) taken with any of Wheeler (U.S. 5,981,501), MacLachlan (WO 99/39741) or Semple (WO 98/51278). Applicants respectfully traverse the rejection, since there is no motivation in the art for making the combination proposed by the Examiner and, in fact, more pertinent prior art overlooked by the Examiner teaches the skilled artisan to do precisely the opposite of the claimed invention.

It is of course well-established law that in order to establish a *prima facie* case of obviousness under §103(a), the Examiner must show some suggestion *in the art* to make the modification or combination necessary to arrive at the claimed invention. *See* MPEP § 2143.01; *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (A showing in the art of a suggestion or motivation to combine prior art teachings "must be clear and particular.")

It is equally well-established law that an Examiner cannot pick and choose from among the prior art teachings in order to reconstruct the claimed invention, while ignoring contrary teachings in the cited art and elsewhere that would undercut such a combination. In this regard, the Federal Circuit has repeatedly held that:

> In determining whether such a suggestion can be fairly gleaned from the prior art, the full field of the invention must be considered for the person of ordinary skill is charged with knowledge of the entire body of technical literature, including that which might lead away from the claimed invention.

In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). The two groups of references relied on by the Examiner are directed to disparate subject matter and have conflicting objectives with respect to immune responses, and therefore provide no clear and particular motivation to combine their teachings. Moreover, a more pertinent prior art reference that the Examiner may have overlooked undercuts any motivation to combine the references as proposed.

As the Examiner admits, neither of the cited Krieg patents includes any teaching, suggestion or motivation to fully encapsulate their immunostimulatory nucleic acids within a lipid particle as presently claimed. [Office Action, p. 11]. Indeed, neither Krieg reference would motivate the skilled artisan to select a particular lipid delivery vehicle any more than one of the myriad other delivery vehicles disclosed therein, including sterols ('199 patent, col. 14), target cell specific binding agents ('199 patent, col. 15), coupling or crosslinking agents such as protein A, carbodiimide, and N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP) ('199 patent, col. 22) and virosomes ('199 patent, col. 22). In fact, the preferred embodiments disclosed in the examples utilize phosphorothioate-modified oligodeoxynucleotides in simple intraveneous solutions. Neither Krieg patent even exemplifies a lipid-based delivery vehicle. Thus, no clear and particular motivation can be drawn from either of the Krieg references to make the combination proposed by the Examiner.

Similarly, as the Examiner previously noted in the context of denying Applicants' priority claim, the stated objective of Semple in reducing clearance of their disclosed therapeutics conflicts with the immune stimulation objectives of the present case and the Krieg references, a fact which also undercuts any proposed motivation to utilize the teachings of

Semple to formulate an immunostimulatory composition. Specifically, the Examiner has admitted that:

> **On the contrary, the parent application, when read as a whole**, clearly envisions **the advantages in utilization of** encapsulated cationic amphiphile/**antisense** complexes **mainly by their lesser clearance response**. The intended application of an encapsulated cationic lipid/antisense DNA . . . neither supports in any way a broader genus of any encapsulated cationic lipid/nucleic acid polymer complexes for use as an immunostimulatory composition, let alone other specific claimed limitations which recites CpG motifs and secretion of a cytokine . . . .

[Office Action mailed 3/27/03, U.S. Appln. S/N 09/649,527, p. 3 (emphasis original)]. The Examiner has taken a similar position in the instant application. [Office Action mailed 12/22/03, p. 5 ("Such particular citation of the elected species, wherein the only usage of the CpG motif is to induce an immune response is not recognized in the parent '954 application."].

The same conclusion applies to the gene therapy (*i.e.*, sequence-specific) therapeutics disclosed in MacLachlan and Wheeler, which also teach to reduce immunogencity and consequent elimination by the host immune system. [*See, e.g.*, MacLachlan at p. 18, lines 11-22; Wheeler at p. 35]. Thus, no clear and particular motivation can be drawn from Semple, MacLachlan or Wheeler to support their combination with the immunostimulatory nucleic acids of Krieg. To the contrary, the disparate objectives of these sequence-specific therapeutic applications undercuts any such motivation to combine. *See, e.g., Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986) (A reference should be considered as a whole and portions arguing against or teaching away from the claimed invention must be considered).

Moreover, the more recent and pertinent teachings in the art directed specifically to the combination of lipids and nucleic acids for immune stimulatory purposes suggest that complexation rather than encapsulation provides a synergistic benefit. *See* U.S. Patent No. 6,693,086 to Dow *et al.* Dow teach that their nucleic acid:lipid complexes are significantly more immunostimulatory than DNA administered alone (*i.e.* naked DNA as exemplified by Krieg), and that DNA from any source when complexed with lipids at low doses can synergize to provide a strong immunostimulatory effect. ['086 patent, col. 10] Thus, the disclosure in Dow

would actually discourage the skilled artisan from pursuing Applicants' encapsulation approach. If anything, Dow demonstrates a clear motivation in the art to combine the immunostimulatory nucleic acids of the Krieg references with the lipid complexes of Felgner and the like as opposed to Applicants' encapsulation approach. *See, e.g. Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990) (The closest prior art reference "would likely *discourage* the art worker from attempting the substitution suggested by the inventor.").

The only motivation to ignore the contrary nucleic acid:lipid complex teachings of Dow and to focus instead on encapsulation of immunostimulatory nucleic acids derives from Applicants' disclosure and the supporting data in the present case, which clearly demonstrate the superiority of full encapsulation of immunostimulatory nucleic acids as described and claimed by Applicants. Of course, reliance on Applicants' disclosure and/or data to contradict contrary teachings in the art is inappropriate in determining obviousness. *See, e.g., In re Glaug*, 283 F.3d 1335, 62 USPQ2d 1151 (Fed. Cir. 2002) ("An inventor's explanation of how the invention works does not render obvious that which is otherwise unobvious."). The Federal Circuit has repeatedly cautioned against "fall[ing] victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed. Cir. 2000). Where, as here, the closest art actually teaches away from Applicants' approach, motivation is clearly lacking to combine the other more disparate art references as proposed. For the foregoing reasons, Applicants respectfully request withdrawal of the Examiner's rejection of claims 1, 3, 5-8, 11, 14, and 16-19 under 35 U.S.C. §103(a) based on the combination proposed above.

The Examiner has also rejected claims 1, 3, 5-12, 14, and 16-19 under 35 U.S.C. §103(a) as being obvious over Krieg (U.S. 6,207,646) or Krieg (U.S. 6,429,199) taken with any of Wheeler (U.S. 5,981,501), Maclachlan (WO 99/39741), Semple (WO 98/51278), or Tam (U.S. 6,086,913) in further view of Meers. The claims are non-obvious over the Krieg and sequence-specific references for the reasons set forth above. The addition of Tam does not change this analysis. Tam is directed to delivery of AAV vectors for gene therapy, and discloses that AAV can be complexed with lipids before contacting with host cells. The lipids serve as a vehicle for introducing the AAV into a cell where the AAV integrates with the host genome. Tam does not

disclose fully encapsulating nucleic acids into lipid particles; nor does it disclose immunostimulatory compositions. As such, Tam does not render the present invention obvious when combined with Krieg and/or the other sequence-specific references discussed above.

The Examiner further cites Meers as teaching the incorporation of an additive therapeutic agent into the lipid particles disclosed in the combined references cited above. As discussed in paragraph 4 of Dr. Hope's declaration filed June 22, 2004, however, Meers does not describe with any specificity the making of lipid/nucleic compositions and does not cure the deficiencies of the other references.

The Examiner also cites McEver (U.S. 5,605,821), Chang (U.S. 2002/0162123), and Boulikas (U.S. 6,030,956) for showing that the concept of encapsulation of nucleic acids in lipids is well-known. As with each of Semple, MacLachlan and Wheeler, however, these references are again directed principally to sequence-specific nucleic acids rather than immunostimulatory nucleic acids and thus are less relevant than the Dow reference overlooked by the Examiner. McEver is directed to methods for the regulated expression of a gene in endothelial cells or megakaryocytes using the P-selectin gene and only briefly refers to the use of lipids to introduce nucleic acids into cells. Boulikas is directed to gene therapy involving the use of lipids to introduce genes of interest to a cell, and does not disclose immunostimulatory compositions or fully encapsulating the genes in a lipid particle. Chang is not even a prior art reference and in any event is also directed to disparate, sequence-specific gene therapy applications. As such, these additional references also fail to correct the contrary teaching of the Dow reference that lipid:nucleic acid complexation rather than encapsulation is the preferred approach for generating synergistic immune responses with immunostimulatory nucleic acids. Without a more relevant citation, one can only conclude that the teachings of the instant specification are the motivation behind the proposed combination. Accordingly, Applicants respectfully request withdrawal of the Examiner's rejection and allowance of the claims.

All of the claims in the application are now clearly allowable. Favorable consideration and a timely Notice of Allowance are earnestly solicited. If the Examiner has any questions or if an interview would be of benefit, the Examiner is encouraged to contact the undersigned representative at the number provided.

Respectfully submitted,

DORSEY & WHITNEY LLP

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Todd A. Lorenz
Registration No. 39,754
Telephone No. (415) 781-1989

DORSEY & WHITNEY LLP
Four Embarcadero Center, Suite 3400
San Francisco, CA 94111
(415) 781-1989 (telephone)
(415) 398-3249 (fax)

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